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CLINICAL RESEARCH

Evaluation of the impact of the recent controversy over statins in France: The EVANS study



Évaluation de l'impact de la controverse récente sur les statines en France

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Received 12 May 2013; received in revised form 30 May 2013; accepted 19 June 2013
Available online 27 September 2013

KEYWORDS

Adherence;
Cost-effectiveness;
Prevention;
Statins

Summary

Background. — The effect of statins on the prevention of cardiovascular events is well-established. However, a recent controversy in France questioned the value of statins, especially in primary prevention.

Aims. — To evaluate the impact of this controversy on patient adherence to statin therapy and its potential clinical impact.

Methods. — All patients on statins were recruited consecutively from consultations over a period of 1 month (from March 2013) by five physicians in three centres. Patient demographics and comorbidities were collected and adherence to statin therapy was evaluated with a questionnaire. We estimated the number of deaths and major cardiovascular events that could be induced per year.

Results. — A total of 142 patients were included: 37 in primary prevention (mean age, 68.0 ± 13.1 years; 41% women); 105 in secondary prevention (mean age, 67.6 ± 12.1 years; 20% women). In primary prevention, 24.3% of patients intended to stop statins versus 8.6% in

Abbreviations: BMI, Body Mass Index; CABG, Coronary Artery Bypass Graft; LDL, Low-Density Lipoprotein; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention.

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MOTS CLÉS

Adhérence ;
Coût efficacité ;
Prévention ;
Statines

secondary prevention ($P < 0.001$). In France, if the percentages of medication discontinuations following the controversy were actually similar to those we found in our survey, 4992 major cardiovascular events, including 1159 deaths, would be induced in 1 year.

Conclusion. — Recent controversy over statins could induce a large proportion of patients to stop their medication and generate a large number of major cardiovascular events.

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Résumé

Contexte. — Les bénéfices des statines sur la prévention des événements cardiovasculaires sont aujourd'hui bien démontrés. Récemment, en France, une polémique a remis en cause l'intérêt des statines, notamment en prévention primaire.

Objectif. — Évaluer l'impact de cette polémique sur l'observance des patients vis-à-vis des statines.

Méthodes. — Tous les patients sous statines ont été recrutés consécutivement en consultations pendant une période de 1 mois (en mars 2013) par 5 cardiologues au sein de 3 centres. Les caractéristiques démographiques, les comorbidités ont été collectées et l'adhérence aux statines évaluée par un questionnaire. Nous avons estimé le nombre de décès et d'événements cardiovasculaires majeurs que cette polémique pourrait engendrer à partir des données actuelles.

Résultats. — Cent-quarante patients ont été inclus: 37 en prévention primaire (âge moyen, $68,0 \pm 13,1$; 41 % femme); 105 en prévention secondaire (âge moyen, $67,6 \pm 12,1$; 20 % femme). En prévention primaire, 24,3 % des patients interrogés ont déclaré avoir l'intention d'arrêter les statines contre 8,6 % prévention secondaire ($p < 0,001$). En France, cette polémique pourrait engendrer 4992 événements cardiovasculaires majeurs dont 1159 décès par an si les patients arrêtaient réellement leur statine.

Conclusion. — La polémique récente sur les statines pourrait entraîner l'arrêt de ces traitements chez de nombreux patients et ainsi provoquer la survenue de nombreux d'événements cardiovasculaires majeurs.

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Introduction

Randomized controlled clinical trials and meta-analyses have shown statins to be beneficial in decreasing morbid and mortal cardiovascular events in apparently healthy individuals and in those with clinically evident cardiovascular disease [1–6]. However, a recent controversy in France questioned the value of statins, especially in primary prevention, in which the cost-effectiveness of treatment is more complex to assess [7–9]. Therefore, we aimed to evaluate the impact of this controversy on patient adherence to statin therapy and its potential clinical impact.

Methods

Patient population

All patients on statins were recruited consecutively from outpatient consultations over a period of 1 month (from March 2013) by five physicians (L.S., L.P., D.B., N.D. and E.P.) in three centres (including two university hospitals and one private centre).

Patients were included regardless of the type of cardiovascular event prevention (primary or secondary).

Data collection

Data were recorded on dedicated questionnaires at each centre by the consulting physicians and entered into a

common database. The following data were prospectively collected and electronically stored for each patient: demographic characteristics (age, sex and body mass index [BMI]), cardiovascular risk factors (arterial hypertension, diabetes, current smoking, hyperlipidaemia) and medical cardiovascular history (presence of prior acute myocardial infarction [MI], prior percutaneous coronary intervention [PCI], prior coronary artery bypass graft [CABG], peripheral artery disease, chronic kidney disease). Chronic kidney disease was defined as creatinine clearance < 30 mL/minute or creatinine > 15 mg/L.

Regarding adherence to statin therapy, for each patient we collected the indication for statin treatment (primary or secondary prevention) and the type, dose, duration and potential side-effects of the statin used.

During the consultation, the physician initially did not allude to the statin controversy, in order to assess whether the patient mentioned it spontaneously; if they did not, the physician asked the patient at the end of the consultation whether they had heard of the controversy. In all cases, patients were asked whether they intended to stop their statin treatment as a consequence of the controversy.

One-year potential clinical impact

For this study, we made the conservative assumption that patients stopping statins would have a 1 mmol/L increase in low-density lipoprotein (LDL) (the average effect of the lowest dose of any statin available is about a 1.5 mmol/L reduction in LDL) [10]. Using the Cholesterol Treatment

Table 1 Baseline characteristics according to type of prevention.

	Primary prevention (n = 37)	Secondary prevention (n = 105)	P
Age (years)	68.0 ± 13.1	67.6 ± 12.1	0.86
Women	15 (41)	21 (20)	0.01
BMI (kg/m ²)	25.8 ± 4.2	26.5 ± 6.8	0.58
Hypertension	31 (84)	60 (66)	0.04
Diabetes mellitus	8 (22)	33 (31)	0.26
Current smoking	2 (5)	16 (15)	0.12
Hyperlipidaemia	30 (81)	75 (74)	0.36
Previous MI	0 (0)	66 (63)	< 0.001
Previous PCI	0 (0)	69 (66)	< 0.001
Previous CABG	0 (0)	20 (19)	0.004
Peripheral artery disease	0 (0)	10 (10)	0.05
Chronic renal insufficiency	9 (24)	18 (17)	0.34

Data are presented as mean ± standard deviation or number (%); BMI: body mass index; CABG: coronary artery bypass graft; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Trialists' collaboration meta-analysis [7] and data from the National Health Insurance System on statin consumption according to the presence of cardiovascular history [11], we evaluated the potential clinical impact of this controversy in terms of cardiovascular events (including death, non-fatal MI or stroke) and cardiovascular death.

In primary prevention, the National Health Insurance System estimated that 8.7% people used statins in France (i.e. 5046 million). Results of the meta-analysis showed a reduction of 1.44 cardiovascular events per 100 person-years on statins (risk reduction, 25% per mmol) and 0.53 cardiovascular deaths per 100 person-years (risk reduction, 15%).

In secondary prevention, the National Health Insurance System estimated that 70.7% people used statins in France (i.e. 1218 million). Results of the meta-analysis showed a reduction of 3.27 cardiovascular events per 100 person-years on statins (risk reduction, 21% per mmol) and 1.76 cardiovascular deaths per 100 person-years (risk reduction, 12%).

Statistical analysis

Statistical analyses were performed using Stata software (version 12; StataCorp LP, College Station, TX, USA) or SPSS software (version 20.0; IBM, Armonk, NY, USA). For quantitative variables, means, standard deviations and minimum and maximum values were calculated. In addition, medians with interquartile ranges were calculated for some variables. Discrete variables are presented as percentages. Comparisons were made using the chi-square test or Fisher's exact test for discrete variables and using unpaired *t*-tests, the Wilcoxon signed-rank test or one-way analyses of variance for continuous variables. Odds and hazard ratios are given with their 95% confidence intervals. For all analyses, a *P* value < 0.05 was considered significant.

Results

Over a 1 month period, a total of 142 patients were included in this study.

Baseline characteristics

Baseline clinical characteristics of patients on statins according to the type of prevention are summarized in Table 1. Most patients were followed for secondary prevention (74%). The mean age was similar in both groups. The proportion of women was higher in primary prevention. In addition, the proportions of diabetes, current smoking, hyperlipidaemia, obesity (BMI > 30 kg/m²) and chronic renal insufficiency were similar in both groups; however, more patients on statins for primary prevention had hypertension.

Participating centres

Patients were enrolled by five physicians (cardiologists) in three hospitals: two university hospitals (the Necker Hospital and the Georges-Pompidou European Hospital, in Paris) and one private centre (in Issy-les-Moulineaux). No significant difference was observed according to centre.

Impact of statin controversy

Overall, 23% of patients spontaneously talked of the controversy over statins during the consultation and 68% were aware of it. No difference was observed in terms of the type of prevention (27% vs 22%, *P* = 0.53 and 62% vs 70%, *P* = 0.75, respectively). In primary prevention, 19% of patients had doubts about the benefits of treatment versus 10% in secondary prevention (*P* = 0.13). Sixty-five percent of patients agreed to take generic drugs and 53% reported reading patient information leaflets for their medications (no difference in terms of the type of prevention).

Table 2 Statin therapy according to type of prevention.

	Primary prevention (n = 37)	Secondary prevention (n = 105)	P
<i>Statins used</i>			
Atorvastatin	11 (30)	31 (29.5)	
Fluvastatin	2 (5)	3 (3)	
Pravastatin	7 (19)	10 (9.5)	
Rosuvastatin	15 (41)	46 (44)	
Simvastatin	0 (0)	15 (14)	
Ezetimibe ^a	2 (5)	9 (9)	
<i>Adverse events: muscular weakness, stiffness or pain</i>	10 (27)	21 (20)	0.37
<i>LDL cholesterol (mg/L)</i>	108 (95–137)	82 (64–101)	<0.001

Data are presented as number (%) or median (interquartile range); LDL: low-density lipoprotein.

^a Alone or with statin.

All patients had statins for primary or secondary prevention (Table 2). Rosuvastatin and atorvastatin were the most commonly used statins, whatever the type of prevention. Ezetimibe was used in 5% for primary prevention and in 9% for secondary prevention. Adverse events (muscular weakness, stiffness or pain) were reported in 27% in primary prevention and in 21% in secondary prevention. The median LDL cholesterol concentration was 108 mg/L (interquartile range, 95–137) in primary prevention and 82 mg/L (interquartile range, 64–101) in secondary prevention.

Finally, 24.3% people using statins in primary prevention intended to stop their medication versus 8.6% in secondary prevention ($P < 0.001$) (Fig. 1). However, very few patients had actually stopped their medication before the consultation. Among these patients, no difference was observed according to age group (<60, 60–74, ≥ 75 years) and 80% were women in primary prevention while 80% were men in secondary prevention.

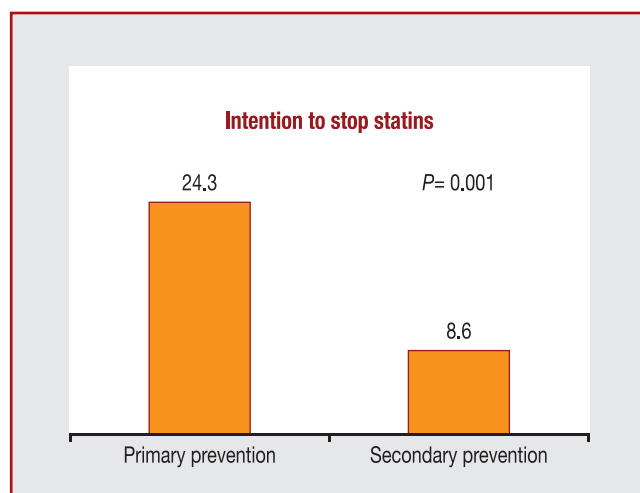


Figure 1. Proportion of patients with the intention to stop statin therapy according to type of prevention.

Patients who intended to stop statin therapy were more often women, had less cardiovascular disease and had more adverse events associated with statins (Table 3).

Potential clinical impact

In primary prevention, on a national scale and based upon the Cholesterol Treatment Trialists' results, one can calculate that 18,000 events are avoided by statin treatment per year, including 3970 deaths. If 24% of patients stopped their medication, 4320 events would be induced, including 953 additional deaths in 1 year.

In secondary prevention, it can be estimated that 8400 events are avoided by statin treatment each year in France, including 2580 deaths. If 8% of patients stopped their medication, 672 events would be induced, including 206 additional deaths in 1 year.

Overall, 4992 events would thus be generated, including 1159 additional deaths in 1 year.

Discussion

The present study demonstrated that a large proportion of patients using statins are at risk of stopping their medication after the recent controversy over statins in France. If they actually did so, this controversy could generate approximately 5000 major cardiovascular events per year, including over 1100 deaths. In addition, our data confirm the impact that media can have on public health issues [10,12,13].

As might be expected, our results showed that the proportion of patients intending to stop statin therapy differed according to the type of prevention. The benefits of statins in secondary prevention after cardiovascular events are well-documented [8,14–17] and statins are recommended with a high level of evidence in the current guidelines [18,19]. In addition, patients are more aware of the potential importance of treatment compared with in primary prevention. Therefore, the proportion of such patients who would stop their treatment was small (<10%).

The use of statins in primary prevention is more complex and the cost-effectiveness is more controversial. Some

Table 3 Baseline characteristics according to intention to stop statin therapy.

	Intention to stop statin therapy (n = 18)	No intention to stop statin therapy (n = 123)	P
Age (years)	67.6 ± 12.6	67.7 ± 12.3	0.48
Women	9 (50)	27 (22)	0.01
BMI (kg/m ²)	23.1 ± 4.0	26.8 ± 6.3	0.01
Hypertension	13 (72)	87 (70)	0.86
Diabetes mellitus	3 (17)	38 (31)	0.22
Current smoking	2 (11)	16 (13)	0.83
Hyperlipidaemia	14 (78)	91 (75)	0.81
Previous MI	5 (28)	62 (50)	0.08
Previous PCI	4 (22)	65 (52)	0.02
Previous CABG	4 (22)	16 (13)	0.30
Peripheral artery disease	1 (6)	9 (7)	0.79
Chronic renal insufficiency	3 (17)	24 (19)	0.79
Adverse events: muscular weakness, stiffness or pain	9 (50)	22 (18)	< 0.001
LDL cholesterol (mg/L)	120 (93–148)	85 (68–104)	< 0.001

Data are presented as mean ± standard deviation, number (%) or median (interquartile range); BMI: body mass index; CABG: coronary artery bypass graft; LDL: low-density lipoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention.

physicians are not convinced that medications such as statins should be used at all for primary prevention, as evidenced by the current debate. This probably explains why one of four patients surveyed wanted to stop their statins after the global media campaign suggesting that these medications could be harmful. Of note, all patients who were ready to stop their treatment reported side-effects (muscular weakness, stiffness or pain), which could encourage them to stop their medication and constitute a confounding factor. However, several sources, including randomized trials and meta-analyses, have demonstrated the benefits of statin therapy in this indication [4,6–9,20]. In the last meta-analysis published in the Cochrane Database [20], which included 18 randomized trials (56,934 patients), Taylor et al. showed that all-cause mortality and fatal and non-fatal cardiovascular events were significantly reduced with the use of statins in primary prevention (9.3% vs 12.2%; relative risk 0.75; 95% confidence interval 0.70–0.81). Of 1000 patients treated with a statin for 5 years, 18 would avoid a major cardiovascular event, which compares well with other treatments used for preventing cardiovascular disease.

The current controversy concerns especially the use of statins in primary prevention for people at low risk of vascular disease. Another meta-analysis of individual data from 27 randomized trials published in The Lancet [8] showed that reduction of LDL cholesterol with statin therapy significantly reduced the risk of major vascular events in individuals with a 5-year risk < 10% (in whom the mean risks were 2.6% for major coronary events plus 3% for other major vascular events), even in those with no previous history of vascular disease, diabetes or chronic kidney disease. In addition, they also demonstrated that statins are indeed both cost-effective and safe for people with a 5-year risk of major vascular events < 10%, which is consistent with other studies [8,21–23]. Statin therapy is

therefore cost-effective in primary prevention, including for people at low risk of vascular disease.

Finally, in the current context of growing suspicion of pharmaceutical companies, patients are becoming more reluctant to use long-term medications. Therefore, it is crucial to inform patients correctly about medical management (to explain the benefit/risk balance for each decision) and to be careful with messages that are given to the population. Regarding statins, the current controversy could be dramatic and could generate a large number of major cardiovascular events. In addition, previous health communication research has documented the importance of the news media's influence on the public's health-related perceptions and health behaviours [10,12,13]. Therefore, our study suggests that future educational efforts, based on unquestionable scientific evidence, may be needed to overcome the politicized context and avoid a negative public health impact.

Our study has obvious limitations. The cohort studied was small and we cannot be certain that it is representative of the French population. However, if anything, it is likely that patients followed by cardiologists are more 'health-sensitive' than patients who do not seek specialist advice; therefore, the impact of the public controversy that we observed might be an underestimation. In fact, in the general population, including numerous people not referred to cardiologists, the controversy might lead to even greater rates of treatment discontinuation than those that we observed. Conversely, to calculate the number of potential major cardiovascular events, we assumed that patients who intended to stop statins had really stopped them and that all other patients continued to take their medication. It is known, however, that about 25% of the patients on statin treatment after an acute MI are poorly adherent to their treatment [24]. Some of the patients who reported having decided to stop their treatment, might

have done so independently of the controversy; this is not likely to be a major confounder, however, as most of our patients had been on statin therapy for a very long time and were good adherers to their treatment up until then. Overall, it is likely that a fair proportion of the patients who reported intending to stop their medication might actually have continued to take it, after considering the advice of their cardiologist. Conversely, stopping one class of medication might also encourage patients to stop other treatments, such as antiplatelet therapy, and then increase the number of major cardiovascular events.

Conclusion

Recent controversy over statins could induce a large proportion of patients to stop their medication and generate a large number of major cardiovascular events. In the present context of suspicion regarding all medications, it is crucial to be careful with messages delivered to the population and to take time to explain to patients the expected benefits of all medications they are prescribed. Future educational efforts may be needed to overcome the inappropriately politicized context of public health issues.

Disclosure of interest

N.D.: received speaking or consulting fees from AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Eli-Lilly, GSK, MSD, Novartis, Novo-Nordisk, Pfizer, Roche, sanofi-aventis, Servier and The MedCo. E.P. received speaking or consulting fees from AstraZeneca, Bayer, Daiichi-Sankyo, Eli-Lilly and Servier. A.S., D.B., L.P., L.S.: none.

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